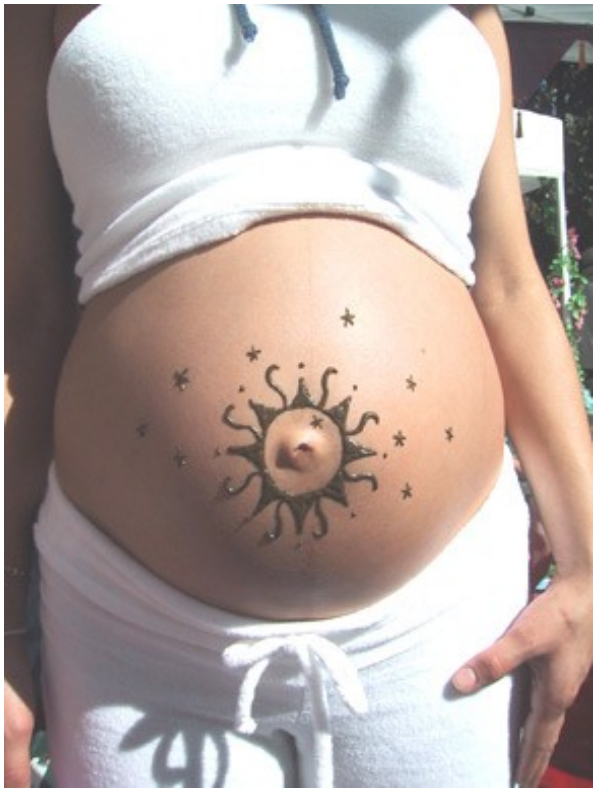
Anesthetic Considerations of Paroxysmal Nocturnal Hemoglobinuria

Elizabeth Javernick
CPT, MC, USA
Walter Reed Army Medical Center

Objectives:

- Case Presentation
- Discuss the pathophysiology of Paroxysmal Nocturnal Hemoglobinuria (PNH)
- Discuss the clinical features, diagnosis, treatment, and prognosis of PNH
- Discuss recommendations for anesthetic management to include considerations in the parturient

Case Presentation—L&D



28 y/o G_1P_0 @ 27+5 wk EGA

PMHx: PNH x10yr
- Hepatic Thrombosis
- Chronic anemia/thrombocytopenia
- Recurrent pyelonephritis

Admitted to Antepartem for acute RUQ pain

S/Sx of pre-ecclampsia

PSHx: Renal stent and Upper GI—no complications

Meds: Lovenox, Cefibuten, PNV, Iron, Folate, Predisone, Vit D, TUMS

All: PCN

PE: 64kg Nml airway/CV/Resp/Gravid Abd +slight jaundice

Labs: H/H 9.2/26.6 Plt 30 elevated LFTs

Paroxysmal Nocturnal Hemoglobinuria

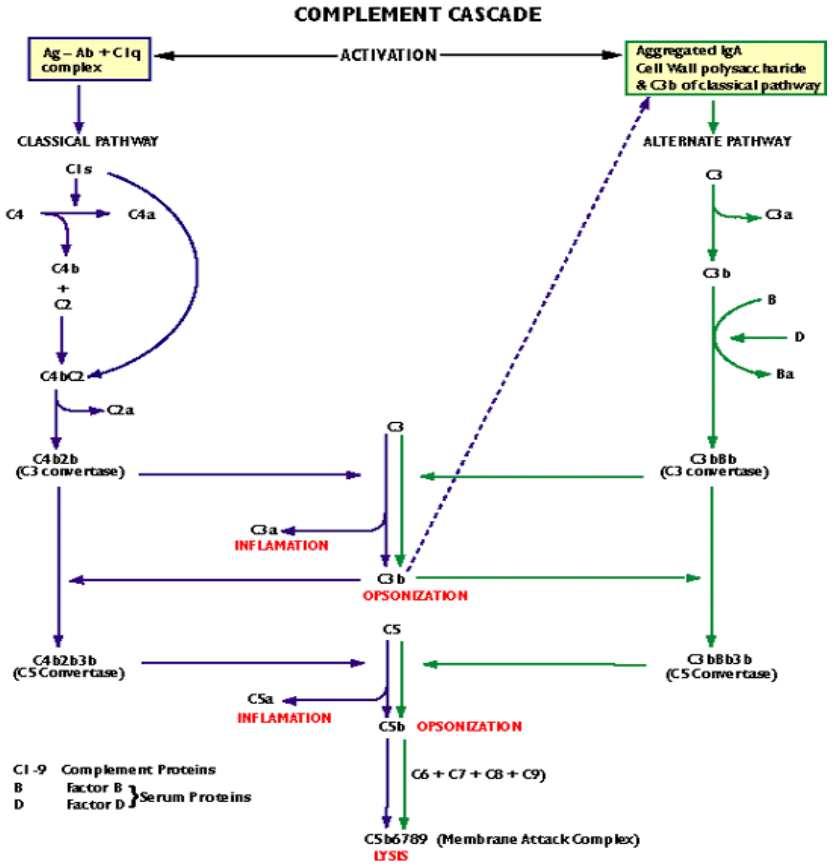
- Rare acquired hematopoetic stem cell disorder
- 1-10 per million
- Most frequent in 3rd decade
- Asian ancestry
- RBCs susceptible to complement-mediated lysis
- Related to lack of cell surface proteins that prevent complement attack

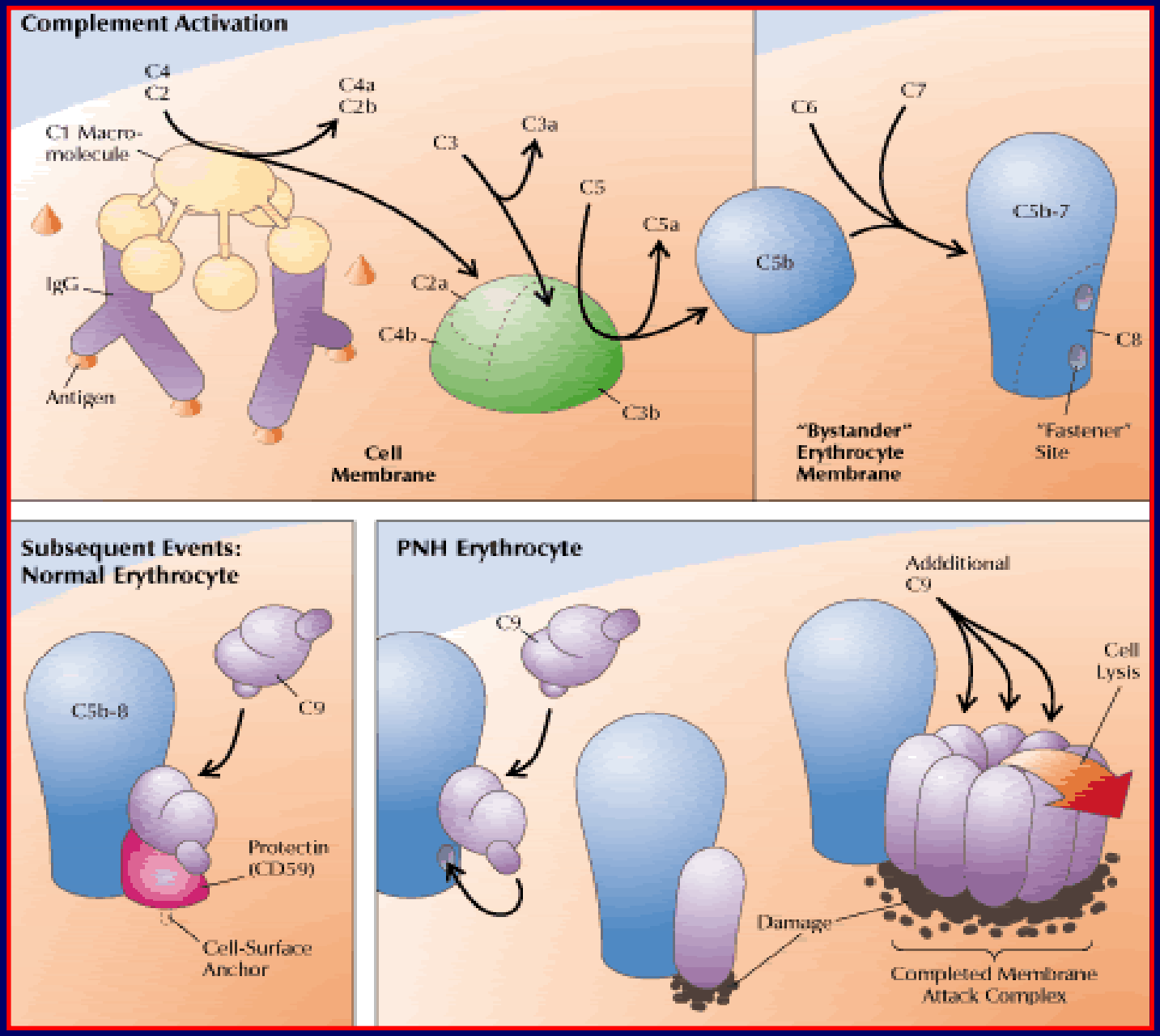
History of PNH


Jack the Ripper

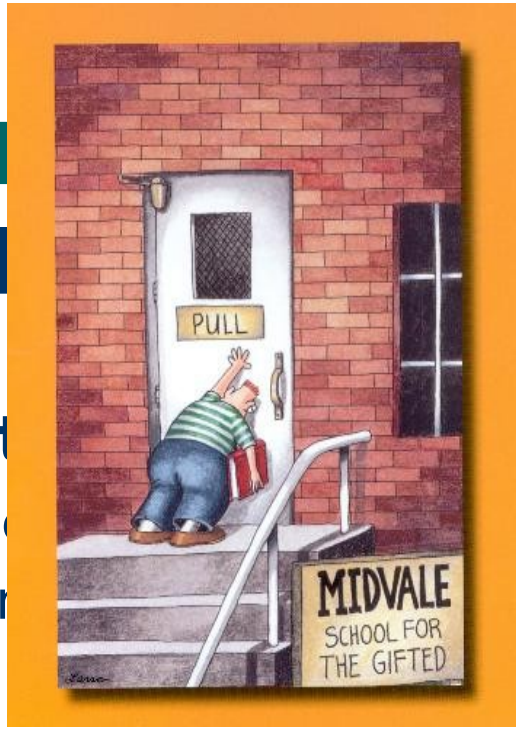
- **1866**—first case report by Gull describing nocturnal hematuria
- **1882—**Strubing recognized PNH as a definite syndrome
- **1925**—Enneking coined the name “Paroxysmal Nocturnal Hemoglobinuria”
- **1930s**—Ham identified the role of complement and developed the serum test which is still used for diagnosis
- **1980s—**PNH blood cells found to lack cell surface proteins
- **1990s—**Somatic mutation identified as *PIG-A* gene

Complement Cascade--review




Complement Activation
C4
C2
C4a
C2b
C1 Macro-
molecule
C3
C3a
C5
C5a
C6
C7
C5b-7
C5b
IgG
C2a
C4b
C8
Antigen
C3b
Cell
Membrane
"Bystander"
Erythrocyte
Membrane
"Fastener"
Site
Subsequent Events:
Normal Erythrocyte
C5b-8
C9
Protectin
(CD59)
Cell-Surface
Anchor
PNH Erythrocyte
C9
Additional
C9
Cell
Lysis
Damage
Completed Membrane
Attack Complex

Pathophysiology of PNH

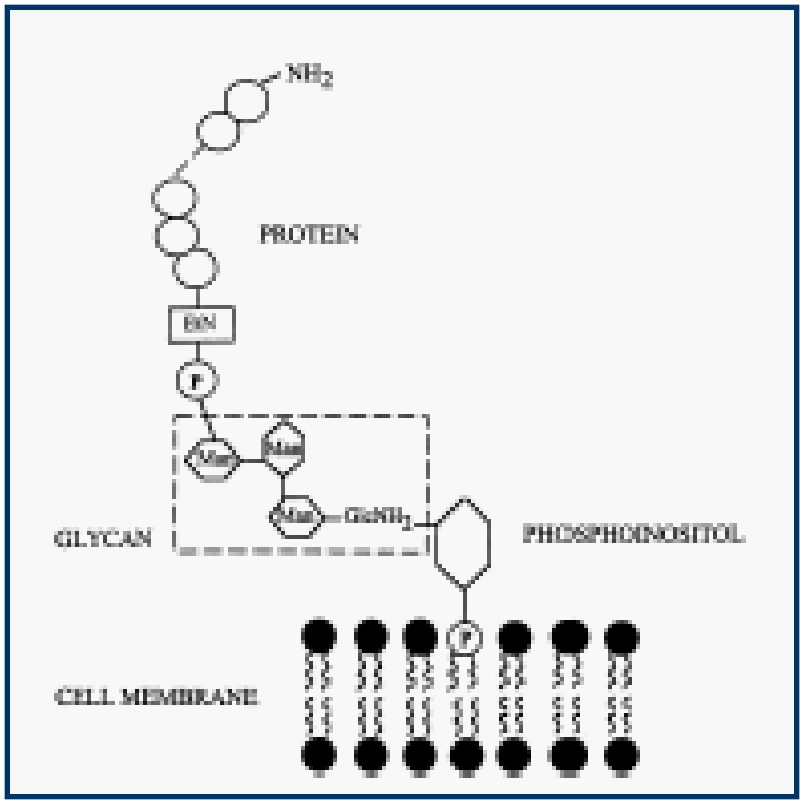


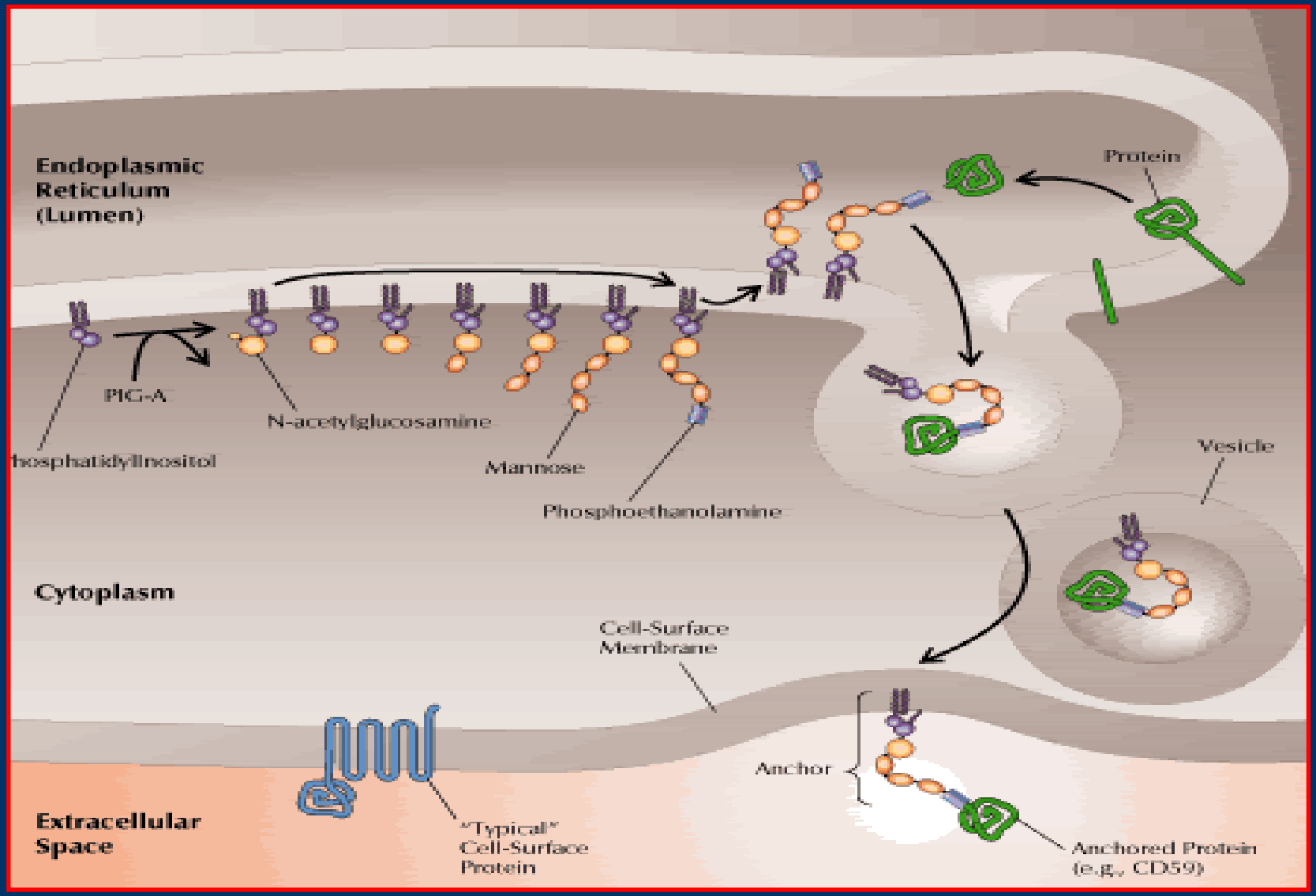
- **Attachment of cell surface prot**
  - transmembrane hydrophobic sequenc
  - anchor embedded within the membra
    that the protein attaches to

- **Common variable in all missing cell surface proteins is Glycophosphatidylinositol (GPI) anchor**

GPI anchor

- Unclear purpose
- Defective biosynthesis at early step
- Coded by the *PIG-A* gene
- Approx 30 GPI-anchored proteins; 20 shown to be deficient in PNH
- All vary greatly in function (enzymes, receptors, and complement mediators)




Endoplasmic Reticulum (Lumen)
Protein
PIG-A
N-acetylglucosamine
hosphatidylInositol
Mannose
Phosphoethanolamine
Vesicle
Cytoplasm
Cell-Surface Membrane
Anchor
Extracellular Space
"Typical" Cell-Surface Protein
Anchored Protein (e.g., CD59)

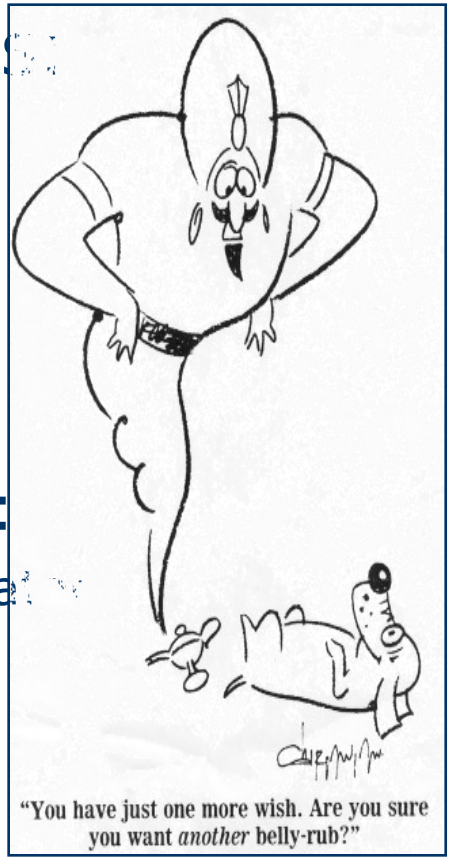
Missing proteins of importance

Complement regulating proteins:

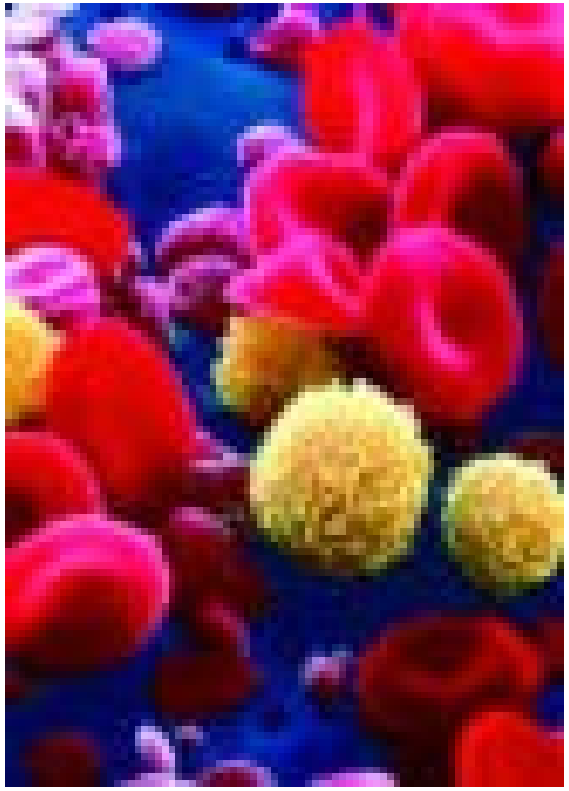
- **CD59** (aka MAC inhibitor/protectin)
- **Homologous restriction factor** (HRF)
- **CD55** (aka decay accelerating factor)

Thrombosis regulating proteins:

- **CD87** (aka urokinase-type plasminogen activa
  receptor)

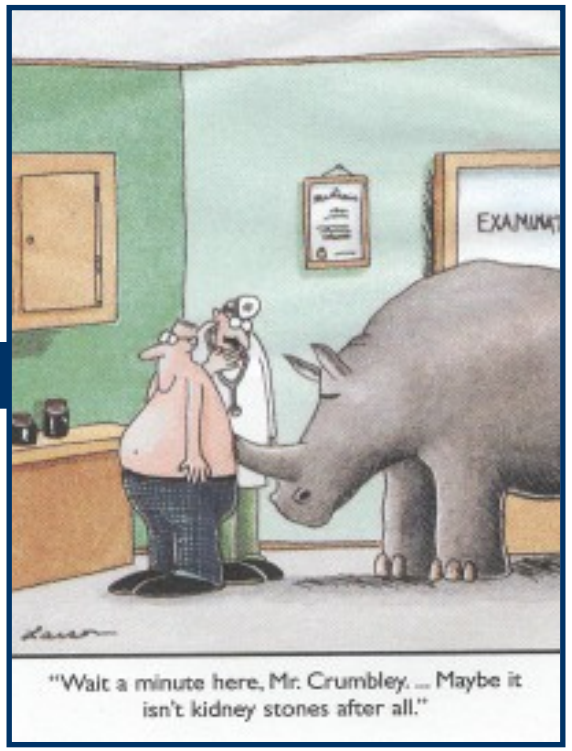


PNH Cell Types



- **Type I**: almost normal cells
- **Type II**: intermediate
- **Type III**: very sensitive
- Type II/III cells bind increased C3—excessive number of MAC are formed
- Can exist in any combination in pts with PNH

Clinical features



- **Highly variable**
- **Classic Triad**
  - Hemolytic Anemia
  - Bone Marrow failure (thrombocytopenia/neutropenia)
  - Venous Thrombosis
- **Chronic course with acute exacerbations**
- **Exacerbations often associated with infection**

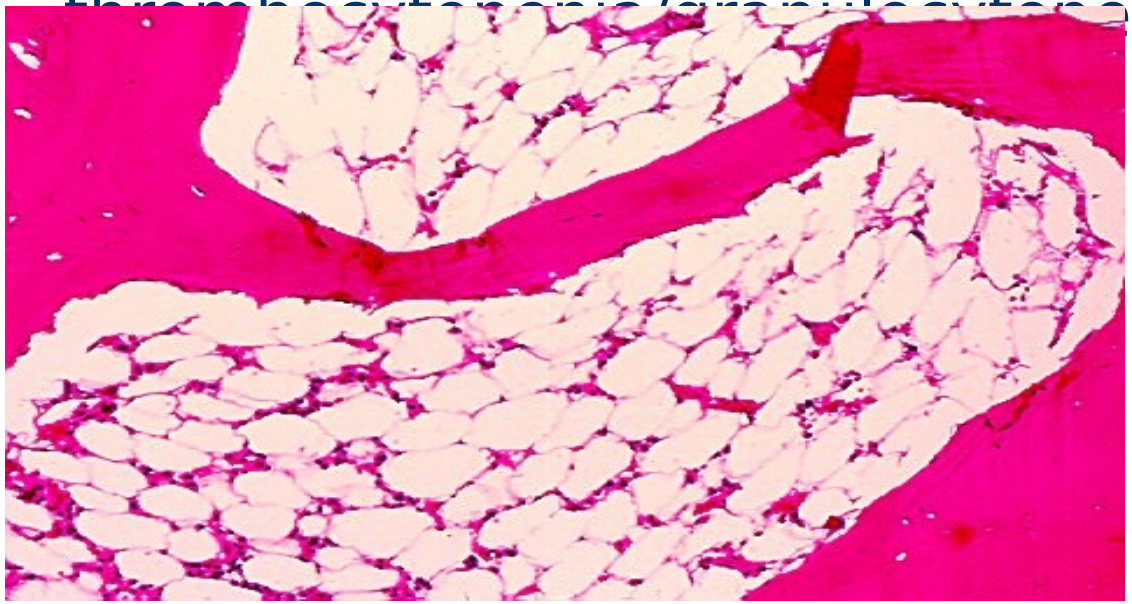
Hemolytic Anemia

- **Present to some degree in all cases**
- **Degree of hemolysis depends on:**
  - Proportion of sensitive RBCs
  - Cell type (PNH I-III)
  - Complement activation (ie infection, allergies, transfusion reaction, etc)

- **Other effects of hemolysis:**
  - Iron deficiency
  - ATN/ARF during episodes of massive hemolysis
  - CRF
  - Esophageal spasm (achalasia-like sx)
  - Impotence

Bone Marrow Failure

- Most severe: aplastic anemia
- More commonly: active BM producing defective cells
- 2/3 – thrombocytopenia/granulocytopenia



Venous Thromboses—the sinister sign

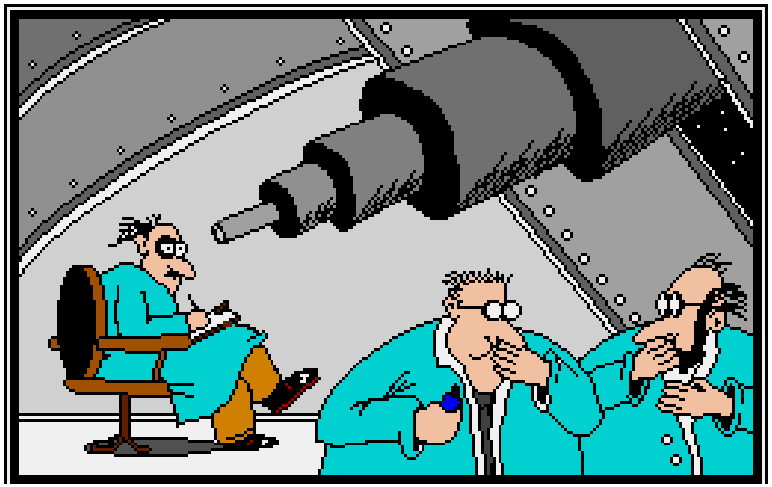
- **20% incidence in Europe and US (lower in Asians)**
- **Mainly central thromboses:**
  - Liver (Budd-Chiari)
    - hepatic veins can thrombose in acute crisis or insidiously
    - Tends to persist with periodic exacerbations/remissions
    - Usually ultimately fatal
  - Cerebral Veins/Sinuses
    - Less common
    - Also tends to persist—Poor prognosis
  - Abdominal Veins
    - Renal/Spleen/Stomach/Intestinal
- **LE DVT more common than in general population, but death by PE rare**
- **Arterial thrombosis also rare**

Diagnosis

- Ham test (acidified-serum lysis test)
  - Gold standard from 1939 until advent of flow cytometry
  - Activation of complement by low pH; PNH cells lyse
  - High specificity
  - Cannot detect varying degrees of RBC sensitivity
- Flow Cytometry
  - Increased level of sensitivity: allows detection of 0.1% GPI-deficient clones
  - Uses monoclonal Ab to missing proteins (CD55/CD59) and fluorescence of labeled cells to detect certain cell populations
  - May screen RBCs, Platelets, and Lymphocyte components

Course and Prognosis

- Life span estimates 10-15yrs
- Approx 25% will survive > 25 yrs
- Spontaneous recovery in ~15% w/o long-term sequelae



Course and Prognosis

- Most common causes of death:
  - consequences of thrombosis (~33%)
  - effects of BM failure (~10%)
- May be preceded by or lead to the development of aplastic anemia (AA)
  - Incidence from various studies of 25-58%
  - Much less risk of thrombosis—less PNH cells overall
  - Possible “natural gene therapy” producing cells which escape destruction in the setting of AA
- 3-5% progress to acute leukemia
  - Likely more related to predisposition in pts with AA, not PNH itself

Treatment

- Focus on 3 aspects:
  - Treat anemia
  - Treat and prevent thromboses
  - Modification of hematopoiesis
- Mainly focused on control of complications rather than interrupting disease process

Treating Cytopenias

- PRBC/Platelet Transfusions
  - Replaces destroyed cells
  - Also suppresses erythropoiesis when done on chronic basis
  - Special transfusion considerations only if necessary
- Epogen/$FeSO_4$/Folate
  - Expensive, but shown to decrease need for high dose steroids and less transfusions
- Glucocorticoids
  - Unknown MOA
  - Useful in 50% pts
  - Thought to be related to direct prevention of hemolysis
  - 0.3-1 mg/kg/day

Treatment and Prevention of Clots

- Prevention
  - Prophylactic anticoagulation for pts w/o contraindications

- Treatment
  - IV/Oral anticoagulants
  - Thrombolytics:

    TPA/Streptokinase/Urokinase

Modifying Hematopoiesis

- **Immunosuppresants**
  - **Better response in pts with hypoplastic marrow than hemolysis**
  - **Mixed results: antithymocyte globulin response rates 0-63%; cyclosporin not effective**
- **Bone Marrow Transplant**
  - Currently most curative and optimal Tx
  - High risk of morbidity/mortality (10-20%)
  - Risk:benefit considering pts with lesser sx
  - No controlled studies for ethical reasons
- **Gene therapy**

Pregnancy and PNH

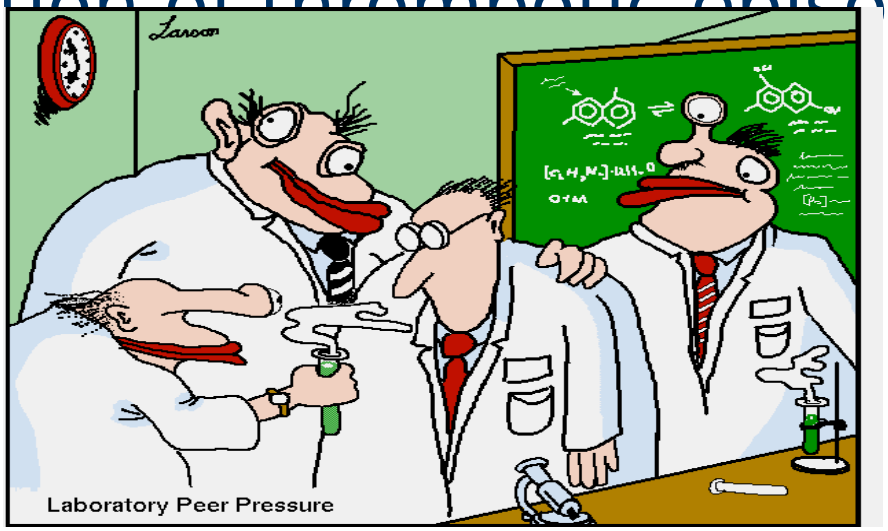
- Maternal mortality **~6-10%** overall; **20%** in setting of thromboembolism
- Fetal loss **~30-40%;** over **50%** preterm (16% higher than healthy parturients)
- Maternal complications **~75%**
  - Most common thrombosis/hemolysis from complement activation
  - Infection rate also higher
- Anemia treated with transfusion/prednisone to maintain **Hg >10** for optimal fetal development
- Folate and Iron supplementation
- Thrombocytopenia treated with platelets
  - Ideally, **>30K** during pregnancy and **>50K** during delivery
- Prophylactic anticoagulation recommended in this population
- Thrombosis treated aggressively
  - Coumadin contraindicated—use **SQ Heparin/Lovanox**
  - Consider **unfractionated Hep** during labor for protamine reversibility
  - Watch for postpartum thrombosis as well

Anesthetic Management

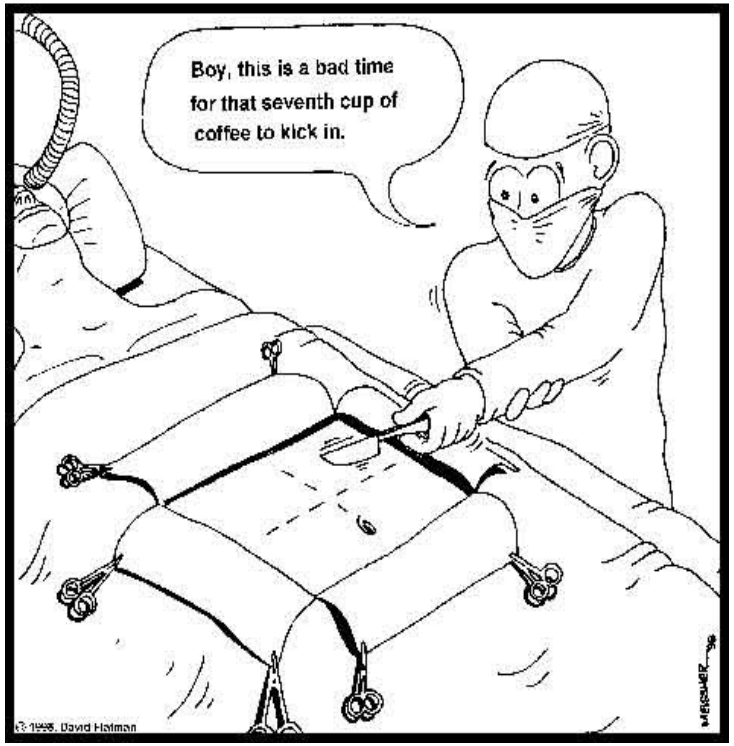
- Scant information in the literature
- 4 general anesthetics; 1 SAB; 1 labor epidural
  - 2 Abdominal Surgeries
  - 3 C-sections
  - Vaginal delivery
- Difficult to establish risks:benefits of anesthetic techniques

Anesthetic Considerations

- Minimize stressors/precipitating factors
- Avoid drugs/techniques activating complement
- Prevention of thrombotic episodes



Anesthetic considerations



- Minimize stressors/precipitating factors:
  - Blunt pain/anxiety responses
  - Appropriate treatment of infections with antibiotics
  - Consider supplemental steroids to avoid hemolytic exacerbations/addisonian crises
  - Avoid factors leading to acidosis: hypoxemia/hypoperfusion/ hypercarbia
  - Keep pt normothermic with active warming techniques

Anesthetic Considerations

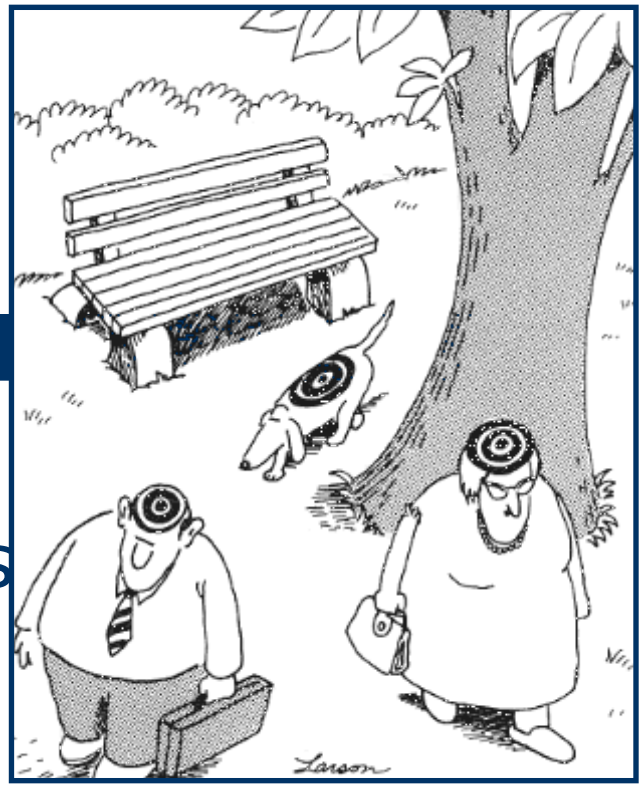
- Avoid drugs/techniques activating complement
  - Nitrous is controversial:
    - Taylor et al. suggested avoiding N2O in pts with hypoplastic anemia and deranged LFTs
    - Kathervil et al. argues that 50% N2O for <8-12hrs causes no sig change in BM and that potential complications can be prevented by pretreatment with folate
  - Suggested that volatile induction may be preferable to IV given lower incidence of anaphylactoid reactions involving complement activation
    - 10% Thiopental reactions associated with complement activation
    - Propofol studies have found no association with complement
    - Overall, classic complement activation in 30% IV inductions

Anesthetic Considerations

- Prevention of thrombotic episodes
  - Acute phase complement proteins reaches max on POD #4
  - Adequate hydration is key to prevention; consider CVP monitoring for blood loss cases
  - No studies on prophylactic anticoagulation; but used by all groups post-op

Monitoring

- Radial A-line—
  serial blood draws
- Minimum large bore IV
  x 1 for any case
- Central line?
  - Bleeding risk in setting of thrombocytopenia vs. need for access/CVP monitoring



How birds see the world

Considerations for the Parturient

- Maintain LUD
- **Neuraxial vs. General—the BIG question!!**
- Pain control
  - Reduction of stress response vs. resp depression
  - Most advocate use of Morphine PCA post-op
- Use of N_2O
  - Consider myelodepression vs. uterine atony at higher doses of volatile

The Parturient

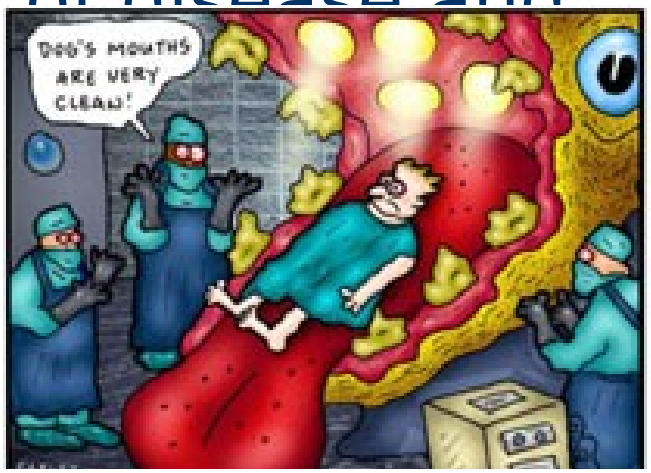
- Case report #1: labor CLE done with plt 69K
  - No clinical bleeding history
  - Argued that a neuraxial block would decrease the complication of thromboembolic event the most:
    - Increased blood flow
    - Increased fibrinolytic activity
    - Reduced platelet adhesiveness and blood viscosity
    - Block of response to maternal stress
  - Started prophylactic Hep SQ 1hr post catheter removal

The Parturient

- Case report #2: Fentanyl PCA during vaginal delivery; GETA for PPH secondary to retained placenta
  - Hx of low platelets requiring transfusion chronically throughout pregnancy (32K on admission for labor)
  - Fentanyl PCA 20 mcg Q5min; additional bolus in 2nd stage
  - Neonatal resuscitation/intubation/narcan
  - RSI for PPH; uncomplicated with min EBL
  - SQ Hep post partum

Conclusions

- Hypervigilance is key: maintain homeostasis
- Each pt requires individual considerations based on the extent of disease and clinical situation



Innovative new designs to make operating rooms more reassur

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